Scholars Academic Journal of Pharmacy (SAJP) **ISSN 2320-4206 (Online)**
Sch. Acad. J. Pharm., 2015; 4(6): 331-336 **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

Review Article

A Retrospective Analysis about the Quality of Therapeutic Drug Monitoring of Digoxin

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Abstract: Since therapeutic range of digoxin is extremely narrow, many patients have been admitted to emergency department due to digoxin intoxication. Therefore, the level of blood digoxin should be followed at frequent intervals in patients who are taking digoxin treatment. In this study, we aimed to evaluate inappropriateness or erroneous practices and to identify their reasons in therapeutic drug monitoring (TDM) of digoxin usage, retrospectively. In this study, we analyzed the results of serum digoxin levels of 1186 inpatients and outpatients from Laboratory Information System (LIS) from January 2013 to July 2015. Results of serum digoxin levels varied from 0.0 nmol/L to 6.9 nmol/L. 47.9% of digoxin levels were in subtherapeutic range, 45.4% of were in therapeutic range, and 6.7% of were in toxic range. Serum digoxin levels were higher in females and in 70-79 ages of patients. TDM of digoxin is useful for enhancing the therapeutic benefits of digoxin and minimizing the incidence of adverse drug reactions. In this study, TDM digoxin usage were evaluated as inappropriate. This was likely due to insufficient information about patient's drug taking time and incorrect timing of collecting the blood samples.
Keywords: Digoxin, therapeutic drug monitoring.

INTRODUCTION

Therapeutic drug monitoring (TDM) is defined as the use of drug measurements in body fluids for an aid to management of patients receiving drug therapy. TDM optimises drug therapy and it is useful for individualization of therapy, thus drug concentrations can maintain within a therapeutic range. TDM is particularly essential for drugs that toxic effects can not easily detect unless they are symptomatic [1]. Therapeutic range is a synthesis of two concepts that the minimum effective concentration for a drug and the maximum safe concentration. When there is a large inter-individual variation between dose and effect, individualising drug dosage is difficult. This is particularly relevant for drugs with a narrow therapeutic range or concentration-dependent pharmacokinetics. TDM involves not only measuring drug concentrations, but also the clinical interpretation of the results. This requires knowledge of pharmacokinetics, sampling time, drug history and the clinical condition of patient. TDM is mostly useful when drugs are used to prevent an adverse effect or to avoid toxicity. For a drug is suitable for TDM, it should satisfy certain criteria such as narrow therapeutic range, significant pharmacokinetic variability, a reasonable relationship between plasma concentrations and clinical effects, availability of cost-effective drug assays [2]. The main aim of TDM is to find out an effective medication against the disease without any dangerous toxic action. When used properly, measurements of drug levels in the clinical setting may provide valuable information. For some drugs there is a close relationship between the level of the drug and its clinical effect [3].

When TDM is used efficiently, it is helpful for many patients. TDM involves many health professionals; laboratory experts, clinical pharmacist, and physicians are all essential to the process, therefore TDM requires a close collaboration between the prescribing physician, the laboratory experts, pharmacist, and patients. Accurate and clinically meaningful drug concentrations can only be obtained by colloboration between these and excellent communication is necessary to ensure that best practice in TDM is achieved. In a large hospital with a high staff turn-over, continuing elucidating about the criteria for rational drug level requests by the members of the TDM team is required [4-6].

Digoxin is a cardiac glycoside that has been used to treat heart failure and arrythmia for many years. Digoxin has inotropic and neurohormonal effects. Positive inotropic effect of digoxin depends on the inhibition of Na^+-K^+ ATPase and secondary activation of the Na^+-Ca^{++} membrane exchange pump resulting in a increased force of cardiac contraction. Neurohormonal effects lead to increased vagal tone, decreased sympathetic tone, decelerated ventricular rate. Although inotropic effects occur at higher digoxin serum levels, neurohormonal effects occur at lower serum digoxin levels [7]. Digoxin is an effective but also highly toxic drug, because digoxin has a narrow therapeutic dose range and can easily reach toxic levels in the blood. Furthermore, digoxin exhibits marked interpatient pharmacokinetic variability. Elevated digoxin levels and clinical toxicity are seen as a common adverse drug reaction. Digoxin toxicity is commonly associated with serum levels > 2.0 nmol/L but may occur with lower digoxin levels if hypokalemia, hypomagnesemia, hypercalcemia impaired renal function or hypothyroidism coexist. Elderly patients, particularly those with impaired renal function and low body weights, are under the greater risk. Therefore, digoxin therapies need to be carefully monitored (8-11). The indications for digoxin TDM include confirmation of clinically suspected toxicity, assessing the reasons for therapeutic failure, assessing the effects of factors which can alter the pharmacokinetics of digoxin. TDM for digoxin was more than 30 years ago and resulted in a marked reduction in the incidence of digoxin toxicity. Laboratory tests based on anti-digoxin antibodies are widely available and significantly support the clinician in monitoring the drug therapy [12,13].

For optimal treatment, serum digoxin concentration alone is not sufficient. Several factors change the tissue reponse to digoxin and must be taken into consideration when interpreting digoxin levels. Hypokalemia is the most common factor which increase the sensitivity of the tissues to digoxin. For this reason, potassium concentrations should always be measured with the digoxin concentrations. Hypercalcemia and hypomagnesemia may also be associated with increased tissue sensitivity to digoxin. Hypothyroidism also increases tissue sensitivity [14,15].

The aim of this study was to analyze appropriateness and inappropriateness in TDM digoxin usage, to improve digoxin TDM usage by identifying inappropriateness and erroneous practices, sunsequently.

MATERIALS AND METHODS

Study Design and Data Collection

The present retrospective study was performed in Kutahya Dumlupinar University Evliya Celebi Research and Education Hospital. The study was carried out in accordance with Declaration of Helsinki.

The TDM of digoxin data were obtained from laboratory information system (LIS). We obtained the 1186 results of serum digoxin measurements between January 2013 and July 2015. These results were belong to inpatients and outpatients who were admitted to the hospital owing to some complaints related to different organ systems (primarily cardiovascular system) and then serum digoxin levels were measured.

Digoxin Measurements

Serum digoxin levels were analyzed based on kinetic interaction of microparticles in solution assay (KIMS) on Roche Cobas C501 autoanalyzer (Roche Diagnostics GmbH, Mannheim, Germany) using original assay reagents.

Therapeutic range of digoxin was 1.0-2.6 nmol/L, subtherapeutic level was below the 1.0 nmol/L, and toxic level was above the 2.6 nmol/L. Laboratory proficiency for digoxin was controlled through two level internal quality control procedurs and intralaboratory precision (CV %) was ranged from 2.2% to 3.2%.

Statistical Analysis

All statistical analyses were performed using SPSS for Windows, version 15.0 (SPSS Inc., Chicago, IL, USA). All data were tested for normality with Kolmogorov–Smirnov test. Continious variables were analyzed with unpaired *t* test and one-way analysis of variance. Bonferroni method was used *post hoc* testing. Categorical variables were analyzed with Chi-square test. The *P* value less than 0.05 were considered statistically significant.

RESULTS

31.6% of patients were male and 68.4% of were female. The age range of patients were from 18 to 95 (mean ± SD, 66.01 ± 13.97). Furthermore, 10.2% of patients were below the 50 age and 12% of were above the 80 age (Table-1).

Serum digoxin levels were higher in 70-79 ages of patients ($P < 0.001$, Table 1). Clinics which requested to blood digoxin levels from patients were various; 65.8% of these were cardiology, 18.7% of these were emergency department, 7.9% of these were internal medicine, 2.9% of these were home care department, 2.5% of these were cardiovascular surgery, and 1.8% of these were the other departments (Table 1). Diagnosis of patients were various; 25.8% of coronary artery disease (CAD), 18.5% of atrial fibrillation (AF), 13.8% of heart failure (HF), 13.7% of diabetes mellitus (DM), 9.7% of hypertension (HT), 5.6 of chronic renal failure (CRF), and 12.9% of the others (Table-1).

Results of serum digoxin levels varied from 0.0 nmol/L to 6.9 nmol/L (mean ± SD, 1.18 ± 0.87). 47.9% of TDM digoxin was in subtherapeutic range,

45.4% of TDM were in therapeutic range, and 6.7% of TDM were in toxic range. Serum levels of digoxin were higher in women than men (P = 0.02) and 75% of patients who had toxic digoxin levels were women (Figure 1, Table 2).

Serum digoxin levels were higher in patients that were diagnosed as CRF. Toxic levels of digoxin were seen in 32.5% of patients with HF, 22.5% of patients with CRF, 13.8% of patients with AF, 7.5% of patients with CAD. Toxic levels were not seen in diabetic patients. Subtherapeutic levels of digoxin were seen in 14.3% of patients with HF, 5.3% of patients with CRF, 17.3% of patients with AF, 25% of patients with CAD and 15.1% of patients with DM (Figure-2).

The number of patients who had toxic levels were 80 and 25% of these were men (N = 20) and 75% of these were women (N = 60) (Table-2). Furthermore, we analyzed some parameters including creatinine, potassium, calcium, and TSH which may affect digoxin levels in 80 patients who had toxic levels. Serum TSH levels were in normal reference range in all patients. Serum potassium levels were in below normal range in 8.8% of patients, in normal range in 70.0% and in high range in 21.3%. Serum creatinine levels were in normal range in 31.2% of patients and in high range in 68.8%. Calcium levels were in low range in 40.0% of patients and in normal range in 60.0% (Table-3).

Table-1: Comparison of blood digoxin levels between demographic and clinical variables of patients

Variables	**Prevalence N (%)**	**Digoksin (nmol/L) mean ± SD**	**Statistical Evulation *P***
Gender			
Male	375 (31.6)	0.85 ± 0.62	P = 0.02
Female	811 (68.4)	0.95 ± 0.71	
Age groups			
< 50	121 (10.2)	0.64 ± 0.61	P < 0.001
50 - 59	167 (14.1)	0.81 ± 0.53	
60 - 69	340 (28.6)	0.91 ± 0.52	
70 - 79	416 (35.1)	1.11 ± 1.01	
80 ≥	142 (12.0)	0.92 ± 0.69	
Department			
Emergency	221 (18.7)	0.95 ± 0.89	P < 0.001
Internal Medicine	94 (7.9)	1.18 ± 0.91	
Cardiovascular Surgery	30 (2.5)	0.76 ± 0.49	
Cardiology	780 (65.8)	0.88 ± 0.57	
Home Care	34 (2.9)	0.78 ± 0.62	
Other	21 (1.8)	1.02 ± 0.90	
Diagnosis			
Coronary artery disease	306 (25.8)	0.85 ± 0.51	P < 0.001
Atrial fibrillation	220 (18.5)	0.90 ± 0.58	
Hypertension	115 (9.7)	0.90 ± 0.74	
Diabetes mellitus	163 (13.7)	0.78 ± 0.48	
Heart failure	164 (13.8)	1.01 ± 0.79	
Chronic renal failure	65 (5.6)	1.29 ± 1.13	
Other	153 (12.9)	0.95 ± 0.82	

Table-2: Distribution of the serum digoxin results according to reference interval and gender.

Therapeutic Range	**Male (%)**	**Female (%)**	**Total* (%)**	***P****	**X^2***
Subtherapeutic	194 (34.1)	374 (65.9)	568 (47.9)	0.134	4.024
Therapeutic	161 (29.9)	377 (70.1)	538 (45.4)		
Toxic	20 (25.0)	60 (75.0)	80 (6.7)		

Table-3: Serum potassium, creatinine, calcium and TSH levels in patients who had toxic digoxin levels

Serum Levels	N (%)
Potassium	
Low	7 (8.8)
Normal	56 (70.0)
High	17 (21.3)
Creatinine	
Low	-
Normal	25 (31.2)
High	55 (68.8)
Calcium	
Low	32 (40.0)
Normal	48 (60.0)
High	-
TSH	
Low	-
Normal	80 (100.0)
High	-

Abbrevations: TSH: Thyroid stimulane hormone.

Serum normal reference ranges; K+: 3.5-5.0 mmol/L, creatinine: female, 0.5-0.90 µmol/L ; male, 0.7-1.20 µmol/L, Ca++: 8.8 -10.2 mg/dL, TSH: 0.30 – 4.0 mIU/L.

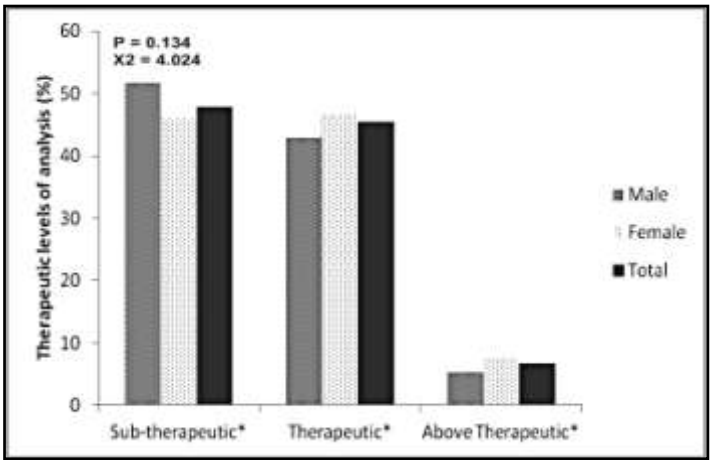

Fig-1: Distribution of the serum digoxin levels according to gender

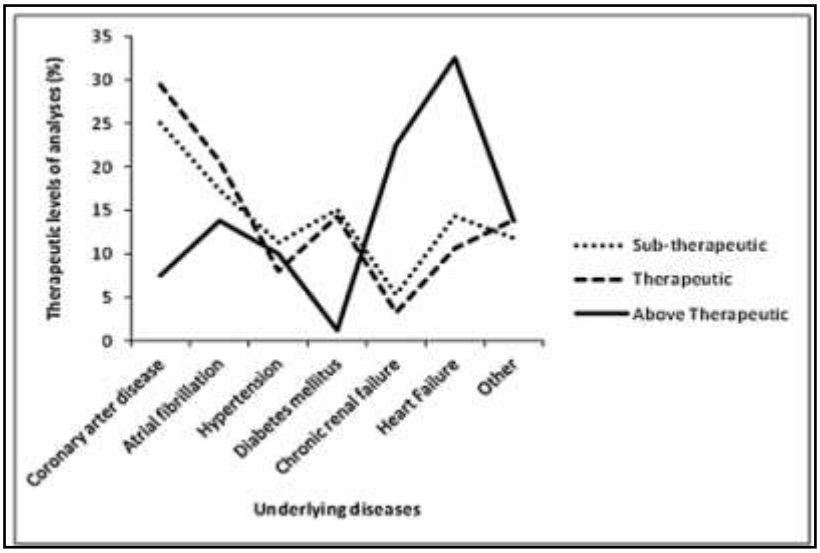

Fig-2: Distribution of the serum digoxin levels according to request indications.

DISCUSSION

TDM for digoxin was introduced more than 30 years ago and resulted in a marked reduction in the incidence of digoxin toxicity. However, despite a long experience of TDM with this drug, TDM is often performed as inappropriate. In literature, inappropriate use of TDM digoxin is quite common. There is often no clear indication for monitoring, the sample is taken at the wrong time resulting in a falsely high or low concentration or an inappropriate clinical action is taken after the result is received [12,16]. Although TDM is an important part of rational drug use and is very useful, many studies suggest that it could be used better and current use is suboptimal. In some studies, up to 70-80% of drug measurements have been inappropriate. Thus, it may be possible to both improve the quality of TDM and reduce the costs of TDM [17,18]. Our study also indicates marked variability in TDM digoxin levels. Our TDM digoxin results were generally insufficient. Subtherapeutic levels of serum digoxin were seen in about half of 1186 patients (47.9%). In a similar retrospective study, digoxin results were insufficient in about half of all cases [19]. In another study by Puche et al. [20] 5623 laboratory tests for digoxin in 2849 adult patients were analyzed and 55.4% of these had inappropriate blood levels of digoxin. In addition, they reported that women were more have high levels of digoxin than men. We also found that serum levels of digoxin were higher in women than men and 75% of patients who had toxic digoxin levels were women [20]. In this study, digoxin levels were more high in 70-79 age of patients. Rich et al. [21] reported that the digoxin levels tended to be higher in older patients consistent with our study [21]. In this study, toxic levels of digoxin were seen in 80 patients (6.7%). Howanitz et al. [22] investigated digoxin TDM in 666 institutions participating in Q-Probes, a quality improvement program of the College Of American Pathologist. 280.000 digoxin levels were evaluated and 6.7% of these had higher levels than 2.6 nmol/L [22]. In a study by Shaker et al. [23], 49.05% of serum digoxin levels were outside of therapeutic range. Serum digoxin levels were out of therapeutic range in 53.12% of patients with HF, in 42.85% of patients with AF consistent with our study (23). In our study, digoxin levels were out of therapeutic range in 45.8% of patients with HF and in 31.1% of patients with AF.

The practice of TDM demonstrates differences between different countries and TDM services have been improved day by day. In Turkey, TDM services started in the late 1980s. In our hospital, TDM service is not exist yet. Blood drug levels are measured by clinical biochemistry laboratory and then results are approved by clinical biochemistry experts. The interpretation of analytical results is a most important part of TDM and interpretation of TDM results by TDM service's experts may have a positive effect on patients clinical outcomes and reduce the adverse effects of drugs [24,25]. The interpretation of TDM results requires knowledge of clinical data, blood collection time, co-administered treatments, drug taking time. The efficiency and cost of routine TDM are questionable when it is requested with no clinical information and sampling times. In order to get meaningful and correct results, samples should be collected after drug have reached steady-state. Drug concentrations can be determined earlier, if toxicity is suspected. Digoxin have extended distribution phases following dosing. This means that if blood is taken too soon after administration, the level will appear to be elevated. Steady-state for digoxin is 5-7 days and samples for digoxin TDM should be take at least six to eight hours after the last dose or ideally before the next dose [6,8,25]. This study has a number of limitations. In our study, we obtained relevant data from our hospital information system (HIS) and LIS, because there were not any detailed request form related to TDM tests. Data were include age, gender, and diagnosis of patients, name and clinic of requesting physician, blood sampling and test analyzing time, but were not include drug taking time of patients. Therefore, we did not have information about the drug taking time of patient and we could not estimated whether subtherapeutic or toxic results were accurate or inaccurate. In a previous study by Mordasini et al. [26], retrospectively 210 digoxin levels were analyzed and 59% of these were found as inappropriate. Their results were mainly due to lack of an adequate indication and due to incorrect timing of collecting the blood samples [26]. Digoxin level monitoring without a proper indication with a wrong sampling time may lead to wrong interpretation of the results and significant unnecessary costs. Huang et al. [27] evaluated the proportion of inappropriate digoxin levels in children at children's hospital. 43.3% of these were considered inappropriate. For the majority of the inappropriate determinations, timing of blood sampling was incorrect (74.6%) [27]. In this study, although inappropriate practices were found, we also seen satisfactory appropriate practices. In patients who have toxic digoxin levels, the other necessary test parameters including potassium, creatinine, calcium and TSH were requested by physicians and these tests were measured by laboratory.

Because of its complex pharmacokinetic profile and narrow therapeutic index, digoxin overdose easily induces adverse events and leads to a fatal outcome, so that TDM of digoxin is useful in enhancing the therapeutic benefits of digoxin and minimizing the incidence of adverse drug reactions but, TDM is only useful, if performed correctly. Three criteria for proper use of digoxin TDM were suggested including proper indications, proper sampling time, and proper interpretation of the measured digoxin level [23,28].

CONCLUSION

As a result, some strategies should be adopted to improve the quality of TDM digoxin in our hospital. First, a TDM service should be established and TDM request form which includes all necessary information

should be prepared. Besides, hospital staff and physicians should be educated. If TDM practices are carried out as multidisciplinary by educated staff team, quality of TDM can be improved.

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